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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,602	DRUILHE, PIERRE	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-9 and 25-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-9 and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/294770.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment filed January 5, 2005 is acknowledged and has been entered. Claims 1, 2 and 10-24 have been canceled. Claims 3, 5, 7-9, 25 and 27 have been amended. New claims 28 and 29 have been added. Claims 3-9 and 25-29 are now pending in the present application. All rejections have been withdrawn in view of Applicant's amendment to the claims and/or comments with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 4, 9, 25-27 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a vaccine composition against malaria comprising a peptide comprising epitopes contained in a MSP-3b peptide (SEQ ID NO: 12), a MSP-3c peptide (SEQ ID NO: 13) or a MSP-3d peptide (SEQ ID NO: 14) or combinations of these peptides and a pharmaceutically acceptable carrier.

Example 6 of the specification (pp. 32-35) sets forth Clinical Studies using MSP-3 with an adjuvant formulation. Example 7 of the specification sets forth Safety Data with immunization of MSP-3 (pp. 35-37). Example 9 of the specification sets forth Immunological Data at page39 and Example 10 discloses

data on the antibody responses at page 40 of the specification. Example 11 of the specification teaches Functional Bioassays (p. 42). "The Long Synthetic Peptide formulation of MSP-3 proved safe: adverse reactions were infrequent, when they occurred they were only localized and not generalized, they were self-resolving, of short duration -generally disappearing within 24 hours-, they did not induce pain and did not led the volunteers to consult: those side-effects, when they existed, were seen only on normal visits. These results are better in terms of safety than those recorded previously using either MSP-1 1.19 in alum or MSP-1 and MSP-2 combinations with Montanide, where severe contro-lateral effects on the previous injection sites, and generalized reactions with fever were recorded. Therefore, the LSP MSP-3 formulation can be considered safer than other vaccine candidates tested so far." (specification, p. 44). Example 12 of the specification teaches Natural passive transfer of antibodies from mother to newborns (pp. 45-46). Example 13 of the specification teaches Studies in cerebral malaria patients (p. 46). Example 14 sets forth In vivo passive transfer experiments in *P. falciparum* infected SCID mice (pp. 47-48). However, none of these examples in the specification sets forth enablement for the claimed vaccine against malaria comprising MSP-3b or MSP-3c or MSP-3d or combinations of these peptides. The specification is not enabled for a vaccine; the examples, as described above, do not set forth in active immunization of an animal or human using the claimed vaccine, followed by a challenge.

The state of the art indicates that at present there are no vaccines that protect against malaria. Arevalo-Herrera et al indicates that because of the complexity of the parasite's life cycle the development of a universal, effective and long lasting vaccine is difficult (p. 444). Arevalo-Herrera et al states that since the use of

whole malaria parasites as vaccines is not feasible, parasite sub-unit vaccines are being envisaged either making use of recombinant technology, peptide synthesis or naked DNA injection. Even though it is accepted that malaria vaccines need to simultaneously target the different parasite developmental stages, most vaccine trials concentrate on individual parasite targets, especially from *P. falciparum*. The of a multi-stage and multi-species vaccine is expected to be advantageous because of simultaneous priming of synergistic immune mechanisms targeting the main parasite species circulating in a given region. (p. 444, col. 2) Arevalo-Herrera et al indicates that even though most efforts towards vaccine development have been focused on *P. falciparum*, development of a worldwide efficient malaria vaccine will require the inclusion of components from two prevalent malaria species, *P. falciparum* and *P. vivax* at least (p. 444, col. 2). Bouharoun-Tayoun et al 2004 states that the study of parasite antigens targeted by ADCI effector antibodies has led to the characterization of MSP-3, a 48 kDa protein present on the surface of the *P. falciparum* merozoite. Cytophilic antibody response against MSP-3 is highly correlated with protective immunity. MSP-3 is currently used as a candidate malaria vaccine in clinical trials (p. 2, col. 1). The art indicates that it is a vaccine candidate but to date no vaccine against malaria using MSP-3, the whole protein or portions of the protein, has been disclosed.

Further, the art teaches problems with other proteins from Plasmodium as vaccine components. Kurtis et al 2001 states that a vaccine is urgently needed to stem the global resurgence of *P. falciparum* malaria; LSA-1 is one of a few proteins known to be expressed by liver-stage parasites, holds particular promise as a vaccine (abstract). Kurtis et al 2001 states that despite "important advances, such as the circumsporozoite protein (CSP)-based vaccine called RTS,S, the goal of a

safe and broadly effective malaria vaccine remains unfulfilled. The parasite's complex life-cycle offers several targets for intervention in the human host and the mosquito vector and vaccines against sporozoite, intrahepatic, blood and sexual stages of the parasite are currently in development." (p. 219, col. 1). As of 2001, there is no effective vaccine that comprises the LSA either alone or in combination with other malaria proteins. Further, because LSA is a liver specific antigen, investigation of its immunological significance is restricted to human studies because no homologue in mouse or non-human primate malarias has been identified (p. 219, col. 1). Others such as Taylor-Robinson et al 2001 have also indicated that LSA-1 may be a good candidate for a vaccine, but no vaccine has been produced that has been shown to be effective (see also Moorthy et al 2004; Ballou et al 2004; Joshi et al 2000; Kurtis et al 1999; Cox 1992; Ntumngia et al 2004; Stowers et al 2001). Shi et al, 1999 indicate that a multicomponent, multistage malaria vaccine can induce immune responses that inhibit parasite development at multiple stages. The rationale and approach used in the development of a multicomponent *P. falciparum* vaccine will be useful in the development of a multispecies human malaria vaccine and vaccines against other infectious diseases (see abstract). "Although studies of immunogenicity and the results of *in vitro* protection experiments have been promising for many of the single stage-specific vaccine candidate antigens, the test of *in vivo* protection has not always been satisfactory. There is consensus, however, that a highly effective malaria vaccine would require a combination of key antigens and/or epitopes from different stages of the life cycle and that induction of both humoral and cellular immunity is required for optimal efficacy. Such a multicomponent malaria vaccine would also circumvent the problems associated with host genetic restriction and

antigenic variability in the case of single antigen-based vaccines." (Shi et al, 1999, p. 1615, paragraph bridging cols. 1-2). Shi et al 1999 also indicates that multiple protective immune responses against multiple antigens from different stages will be needed to protect against malaria (p. 1618, col. 2). "Although a single-antigen and/or stage-specific vaccine could provide protection against infections, there are several reasons to advocate a multivalent, multistage malaria vaccine. A major concern with a single antigen-based vaccine is that an antigenic variant population of the parasite not recognized by the vaccine will cause infection (with heterologous parasites) and cause disease." (see p. 1618-1619).

In view of the fact that the specification does not set forth any enablement with regard to direction or guidance and the absence of working examples for the claimed vaccine composition, and the fact that the state of the art teaches that there are no single antigen (MSP-3b peptide or MSP-3c peptide or MSP-3d peptide or combinations of these peptide) or stage specific vaccines against malaria and the unpredictability and difficulty in obtaining an effective vaccine directed against malaria comprising the claimed peptides there would be undue experimentation necessary for a person of skill in the art to practice the claimed invention.

The rejection is maintained for the reasons of record. Applicant's arguments filed January5, 2005 have been fully considered but they are not persuasive. Applicant has asserted that the only conclusion that can be drawn from the cited references is that they are not relevant to the subject matter of the claimed invention. However, it is noted that the references were cited to give a review/information on the state of the art with regard to vaccines against malaria and the difficulty in developing a vaccine against malaria. The claims generically

recite "vaccine against malaria"; none of the claims recite any specific Plasmodium species that causes malaria. Both *P. falciparum* and *P. vivax* are parasites that cause malaria in humans. Applicant has asserted that the Examiner is misinterpreting the claims to recite a commercialized vaccine and that the claims solely recite a vaccine. Applicant asserts that the sole criteria of a vaccine is to stimulate an immune response that can prevent an infection or create resistance to an infection or to reduce the parasite load or reduce or eliminate parasite replication or growth after invasion and that T-cell and antibody responses are indicative of an immune response. With regard to applicant's arguments, it is noted that the claims are interpreted as broadly as possible. The claims do not specify any particular characteristics or properties for the vaccine, only that it is a vaccine against malaria. Further, it is noted that stimulation of an immune response does not equate to vaccine protection.

On page 14 of the response Applicant lists the results from the clinical trials; however none of these are clearly indicative that the claimed peptides either alone or in combination will protect against malaria. An immune response is not protection against infection. Applicant cited Singh et al (Annex II) and Meraldi et al (Annex III) to clearly demonstrate the success of the presently claimed invention in human studies. However, it is not clear that the peptides were tested individually claimed to protect against malaria. The rejection is maintained for the reasons of record.

4. Claims 3-7 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Oeuvray et al 1994 (Blood, 1994, 84/5:1594-1602) or Oeuvray et al 1994 (Mem. Inst. Oswaldo Cruz, Rio de Janeiro, 1994, 89/Suppl. II:77-80).

Oeuvray et al 1994, for example, discloses the peptides, MSP-3a, MSP-3b and MSP-3c and a pharmaceutically acceptable carrier (abstract; materials and methods). The prior art discloses the specific amino acid sequences as set forth in SEQ ID NO: 11, SEQ ID NO: 12 and SEQ ID NO: 13 (p. 1595, col. 1). The prior art anticipates the claimed invention.

It is noted that the recitation of "vaccine" in claim 4, for example, is viewed as intended use. The recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Since the Patent Office does not have the facilities for examining and comparing applicants' compositions with the compositions of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed compositions and the compositions of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

The rejection is maintained for the reasons of record. Applicant's arguments filed January 5, 2005 have been fully considered but they are not persuasive. Applicant has asserted that neither of the references disclose SEQ ID NO: 11 to 14, and that only SEQ ID NO: 12 is disclosed. However Oeuvary et al (Blood, 1994) discloses SEQ ID NO: 11-13. Applicant has asserted that the MSP-

3a and MSP-3c sequences are not the same as those presently claimed because there is a one amino acid difference. It would appear that they are the same or an obvious variant of the peptide. The function of the peptide is not altered since the prior art peptides are immunogenic. Applicant has asserted that neither reference discloses the MSP-3d, which is SEQ ID NO: 14. However, the claims indicate that the composition comprises one peptide (i.e. MSP-3c or MSP-3d) *or* a combination of said peptides. Therefore the prior art discloses the claimed invention.

With regard to Applicant's assertion that the art does not disclose an immunogenic composition or vaccine, it is noted that the recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

5. Claims 3 and 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oeuvray et al 1994 (Blood, 1994, 84/5:1594-1602) or Oeuvray et al 1994 (Mem. Inst. Oswaldo Cruz, Rio de Janeiro, 1994, 89/Suppl. II:77-80) taken with Saul et al 1999 (Vaccine, 1999, 17:3145-3159).

Oeuvray et al 1994, for example, teaches the peptides, MSP-3a, MSP-3b and MSP-3c and a pharmaceutically acceptable carrier (abstract; materials and methods). The prior art teaches the specific amino acid sequences as set forth in SEQ ID NO: 11, SEQ ID NO: 12 and SEQ ID NO: 13 (p. 1595, col. 1). The prior

art teaches the claimed invention except for the composition comprising alum and/or Montanide.

However, Saul et al teaches malaria a composition comprising a *Plasmodium falciparum* protein formulated in Montanide (abstract; materials and methods). The *Plasmodium falciparum* protein used in the composition was a merozoite surface protein, MSP-1 and MSP-2, similar to the MSP-3. Mice were injected i.m. and s.c. (p. 3148, col. 1) and humans were immunized with 4 micrograms of antigen (p. 3148). It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the components as set forth in either Oeuvray et al and Saul et al 1999 for the preparation of an immunogenic composition comprising peptides of the MSP-3 protein and Montanide as the adjuvant. Both references discuss the need for compositions to treat malaria, which is how the claimed composition would be used. The prior art of Oeuvray et al (either reference) taken with Saul et al 1999 teach the claimed invention, absent any convincing evidence to the contrary.

6. Claims 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "consisting of combinations of peptides of a MSP-3b peptide (SEQ ID No: 12), a MSP-3c peptide (SEQ ID No: 13) and a MSP-3d peptide (SEQ ID No: 14)". It is not clear what Applicant intends by the recitation of "combinations" . Is there more than one combination of peptides possible? The recitation of "consisting" means that all three peptides (SEQ ID NO: 12-14) must be present as the immunogen. Clarification is requested.

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
March 15, 2005